



Jelena Pavlovic treats people with migraines at the Montefiore Medical Center, New York City.

The gender gap

Sex differences in migraine prevalence have been recognized for centuries, but researchers are just beginning to understand the factors that put women at greater risk. **By Michael Eisenstein**

Women are two to three times more likely than men to have migraines. The condition typically hits women hardest in their thirties, when the consequences of days lost to debilitating pain can be tremendous. “This is when women are going through pregnancy and post-pregnancy, taking care of small children and working at their jobs,” says Jelena Pavlovic, a neurologist at the Montefiore Medical Center in New York City. “It’s a time when one builds capital for the rest of their life.”

For more than half of women aged between 18 and 60, the onset and timing of migraines

is connected with the hormonal flux of their menstrual cycle. This relationship is well-documented in the literature, according to Anne MacGregor, a clinician specializing in headache and women’s health at Barts Health NHS Trust in London. “There’s been an understanding of this link for centuries,” she says. And yet little research has been done to explore the nature of sex-related differences in migraine or their clinical consequences.

Much of this knowledge gap is attributable to gender bias – a pervasive problem in clinical research. “If migraine affected men at the same rate, we would have much better studies,” says Pavlovic. “A lot of the biases and

stigma associated with migraine have to do with it being a disorder of women.” But it is also an undeniably thorny scientific problem, requiring a better understanding of the physiological mechanisms underlying migraine and how hormones interact with these pathways to make women more susceptible to this condition.

A vicious cycle

Young boys and girls are about equally likely to develop migraine. But at puberty, the prevalence in females rapidly escalates. Through adulthood, migraine risk increases in everyone, but it continues to climb more steeply in women. Their risk peaks at around age 35, then gradually tapers off until it declines steeply at menopause. In all, the prevalence of migraine in women is estimated to be around twice that of men.

In 1972, clinician Brian Somerville, then at Prince Henry Hospital in Sydney, Australia, published the first study tying shifts in female sex hormones to migraine headaches¹. It has since become clear that the rise and fall of oestrogen is a particularly important driver in this process. “It’s not the absolute levels of hormones, but more the fluctuations in hormones that cause the migraine attacks,” explains Antoinette Maassen van den Brink, a pharmacologist at the Erasmus University Medical Center in Rotterdam, the Netherlands.

The tight coupling between migraines and the menstrual cycle was documented in the US-based Study of Women’s Health Across the Nation (SWAN), which used what Pavlovic calls hormone diaries to identify patterns that correlate with menstrual migraine. “About five days prior to the onset of bleeding, that’s when the oestrogen drops – and that drop is related to this triggering of migraine,” says Pavlovic, who is part of the SWAN team. She says that such rises and falls become especially dramatic during the perimenopause – the period before the complete onset of menopause – when oestrogen levels fluctuate wildly. This causes irregular menstrual cycles and the onset of more frequent and erratic migraine episodes. It can last for several years, or even a decade.

This interplay can complicate hormonal treatments. For example, oral contraceptive prescriptions typically include a seven-day span of in which pills should not be taken or placebo pills are provided instead, setting the stage for a migraine-inducing period of oestrogen withdrawal. MacGregor also notes that some people who receive hormone replacement therapy to mitigate symptoms associated with the onset of menopause risk aggravating their migraines. “There is a myth that as you go into menopause, oestrogen

levels simply decline, but they don't – they can spike super high and fluctuate considerably," she says. "The consequence of those fluctuations is migraine." In that context, hormone replacement therapy has the potential to exacerbate this effect in women with particularly erratic shifts in oestrogen production.

Oestrogen administration also seems to boost the rate of migraine in transgender women. Only a handful of studies have been published, but one Dutch report² found that 26% of individuals undergoing male-to-female transition reported migraine – similar to the 25% prevalence in cis women of the same age group, and much greater than the 7.5% in cis men. Conversely, MacGregor notes that trans men actually have a lower risk of migraine than cis women, potentially because of testosterone's ability to counteract the influence of oestrogen on headaches.

Spot the difference

Oestrogen alone does not fully explain sex differences in migraine. Last year, neuroscientist Greg Dussor at the University of Texas at Dallas discovered striking differences in how male and female rats respond to a signalling molecule called calcitonin gene-related peptide (CGRP)³. CGRP has become a major focus for migraine therapeutics, with multiple inhibitors now approved (see page S4).

Dussor originally sought to replicate findings showing that direct administration of CGRP to the meninges – protective membranes surrounding the brain – is insufficient to sensitize animals to migraine. Like much of the pain research done in animals to date, these findings came from experiments conducted solely in male animals – a problematic practice born of a desire to avoid the 'complexity' of female hormonal cycles. After replicating the findings in male rats, Dussor followed up with parallel experiments in female rats, expecting little difference. "It was supposed to be a control experiment," he says. Instead, his team observed clear sex-specific differences – CGRP elicited a potent pain response in females at doses that had no effect on males. Dussor emphasizes that this does not mean that CGRP-targeting drugs are likely to fail in men with migraine. "It may be that CGRP just works in females at much lower concentrations than it does in males," he says.

There is also evidence that CGRP activity could tie into sex-hormone signalling pathways. For example, Pavlovic notes that high levels of oestrogen seem to correlate with high levels of CGRP – even though migraine events are typically associated with drops rather than increases in oestrogen. Maassen van den Brink has seen similar evidence of interconnected

activity in her studies of people with migraine, but the nature of the interaction remains unclear. "There may be a synergistic effect between the two," she says.

The cardiovascular system is also thought to play a part in migraine pathology, and here too, sex seems to matter. Gisela Terwindt, a neurologist at Leiden University Medical Center in the Netherlands, notes that people with migraine are at greater risk of stroke and myocardial infarction. This is particularly true for migraine with aura, in which people experience neurological symptoms such as visual disturbances. Terwindt notes that the likelihood of stroke is roughly double in these people. Although the absolute risk remains low, it is nonetheless concerning given that migraine typically affects women under the age of 45. And the danger can be further exacerbated in women with migraine who smoke and take oral contraceptives – a combination that can increase the risk of stroke by as much as 34-fold⁴. "That combination of three factors is extremely important for these young women," says Terwindt.

"I've been working in this field for 30 years, and sometimes I still feel like I'm banging my head against a brick wall."

Although the effects of sex hormones are far reaching, they are not the only relevant factor in migraine. "Lower oestrogen levels can trigger migraines, but I think that it is not because of the hormones that you develop migraines," says Nasim Maleki, a psychiatry researcher at Massachusetts General Hospital in Boston. She thinks that perturbations in brain development, particularly during the period of rapid synapse formation and pruning during puberty, might create structural and functional conditions that predispose certain people to migraines. In this context, hormonal flux over the menstrual cycle could end up simply being the trigger that tips women into a migraine state.

A level field

Migraine research is finally taking greater account of sex differences. Since 2016, research funding from the US National Institutes of Health has required that grant recipients take sex into account as a variable in human and animal studies. Dussor says that the field is now generally recognizing that "female animals are actually not that much more complicated to work with".

Terwindt says that funding specifically

for exploring sex differences in migraine is growing. Nevertheless, few investigators are actively engaged in unpicking the determinants of migraine risk in women, and interest from the broader research community remains limited. "I've been working in this field for 30 years, and sometimes I still feel like I'm banging my head against a brick wall," says MacGregor. Ironically, this research is also being hampered by a lack of male participants for comparison. "We have a really hard time recruiting men for our studies," says Maleki, who notes that myriad social, cultural and psychological factors might contribute to sex-related differences in how people cope with migraine or decide to seek care. "There's some stigma attached to pain disorders," says Maleki. "My guess is that women are more OK with seeking help and being open about it."

These knowledge gaps pose a problem for women looking for sound medical advice. Various health organizations have strongly discouraged doctors from prescribing oral contraception to women who have migraine with aura owing to the increased risk of stroke, but Pavlovic points out that this is largely based on an outdated mode of birth control. "It came into existence at a time when the doses of exogenous oestrogen that were available in the market were 50 and 100 micrograms," she says. "But a majority of women today are on 10, 20, or 30 µg." She and her colleagues are now looking to reassess these guidelines. However, Terwindt notes that many general practitioners remain unaware of the aura-associated risk of stroke, and prescribe oral contraception as a stabilizing treatment for migraine without full knowledge of the risks or clear evidence of the benefits. "It's just trial and error," she says. She and Maassen van den Brink have launched a study to establish more firmly whether hormonal treatment helps manage migraine.

But even if this information is slow to percolate out into the medical community, Maassen van den Brink thinks that many women ultimately stand to benefit from the ongoing progress in understanding the influence of hormones on migraine. "If we are able to unravel what these hormones are doing, it would be a magnificent gain in women's health, because we could now reduce their level of migraines to that of males," she says. "The potential is enormous."

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